Synthesis and Physical Properties of Normal Higher Alcohols. II. Synthesis of Normal Higher Primary Alcohols of Odd Carbon Numbers from Heptacosanol to Heptatriacontanol

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In continuation of the work described in the preceding paper[1], synthesis of the normal higher primary alcohols of odd carbon numbers containing from twenty-seven to thirty-seven carbon atoms were undertaken and gave the desired products as pure as practicable.

Heptacosanol was prepared by Bowman's method[2], which was outlined in the first paper[1], from arachidic acid and ethyl ε-bromocaproate. The reaction is shown in the following equations.

$$\underset{\text{(I)}}{C_2H_5O_2C(CH_2)_nBr} \xrightarrow{\text{Ethyl malonate}}$$

$$\underset{\text{(II)}}{C_2H_5O_2C(CH_2)_nCH(CO_2C_2H_5)_2} \xrightarrow{C_6H_5CH_2OH}$$

$$\underset{\text{(III)}}{C_6H_5CH_2O_2C(CH_2)_nCNa(CO_2CH_2C_6H_5)_2} \xrightarrow{RCOCl}$$

$$\underset{\text{(IV)}}{C_6H_5CH_2O_2C(CH_2)_nC(CO_2CH_2C_6H_5)COR} \xrightarrow{H_2}$$

$$\underset{\text{(V)}}{HO_2C(CH_2)_nC(CO_2H)COR} \xrightarrow{-CO_2}$$

$$\underset{\text{(VI)}}{RCO(CH_2)_{n+1}CO_2H} \xrightarrow{\text{Huang-Minlon}}$$

$$\underset{\text{(VII)}}{R(CH_2)_{n+2}CO_2H} \xrightarrow{C_2H_5OH}$$

$$\underset{\text{(VIII)}}{R(CH_2)_{n+2}CO_2C_2H_5} \xrightarrow{LiAlH_4} \underset{\text{(IX)}}{R(CH_2)_{n+3}OH}$$

By means of the same series of reactions but starting with higher fatty acids and ω-bromoacids, higher alcohols than heptacosanol were synthesized. Since the use of ω-bromoacids is restricted by the difficulty of their preparation in pure state when the carbon chain is considerably long, the author has used a series of long chain fatty acids along with the ω-bromoacids I where n is 5, 7 and 10.

The three bromoacid ethyl esters required for condensation with ethyl malonate were prepared by the following methods. Ethyl ω-bromocaproate was obtained by the method described in the first paper. Ethyl ω-bromooctanoate was prepared, with some modification, according to Hunsdiecker's method[3]. Silver salt of ethyl hydrogen azelaate was added to the carbon tetrachloride solution of bromine in reverse of the customary procedure. The yield was 80% which was better as compared with those of the analogous synthesis of Hunsdiecker (69.7%).

Ethyl ω-bromoundecanoate was obtained from undecylenic acid by addition of dry hydrogen bromide in the presence of benzoyl peroxide followed by exhaustive esterification, according to Jones' method[4].

Besides commercially available fatty acids, the long chain fatty acids such as arachidic (C_{20}), tricosanoic (C_{23}), tetracosanoic (C_{24}) and pentacosanoic (C_{25}) acids were synthesized from octadecyl bromide, heneicosyl bromide, and docosyl bromide by repetition of the modified malonic ester synthesis[5].

The condensation products of benzyl alkanetricarboxylates with acid chlorides were semisolid brown materials which were subjected to

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* Some parts of this wark were performed at the Department of Chemistry, Faculty of Science, Kyoto University; Sakyo-ku, Kyoto.

[1] A. Watanabe, This Bulletin, 32, 1295 (1959).

[2] R. E. Bowman, *J. Chem. Soc.*, **1950**, 174.

[3] H. Hunsdiecker et al., *Ber.*, **75B**, 29 (1947).

[4] R. G. Jones, *J. Am. Chem. Soc.*, **69**, 2350 (1947).

[5] W. Bleyberg et al., *Ber.*, **64**, 2506 (1931).

TABLE I

Alcohols	Formula	Calcd.		Found		m. p., °C	f. p. °C	t. p. °C
		C	H	C	H			
Heptacosyl	$C_{27}H_{56}O$	81.74	14.23	81.59	14.36	80.5(81.0)[a]	80.0	7.25
Nonacosyl	$C_{29}H_{60}O$	82.10	14.24	81.30	14.03	83.5(83.8)[b]	82.5	75.0
Hentriacontyl	$C_{31}H_{64}O$	82.22	14.25	81.97	13.95	87.0(87.0)[b]	85.8	78.5
Tritriacontyl	$C_{33}H_{68}O$	82.42	14.25	82.19	14.35	88.5(88.6)[b]	87.8	
Pentatriacontyl	$C_{35}H_{72}O$	82.60	14.26	82.83	14.01	91.2(91.5)[b]	89.5	
Heptatriacontyl	$C_{37}H_{76}O$	82.75	14.27	82.92	14.15	92.7	91.6	

Melting points are uncorrected.

When a sample is cooled below its freezing point, transition appears with change of the transparent waxy material into opaque crystalline state. Transition points of C_{33}, C_{35}, C_{37} alcohols could not be observed.

a) S. Shiina, *J. Soc. Chem. Ind. Japan* (*Kogyo Kwagaku Zasshi*), **39**, 345 (1936).

b) R. G. Johns, *J. Am. Chem. Soc.*, **69**, 2350 (1947).

TABLE II

Ethyl alkane-tricarboxylates	Acid chlorides	Cno.	Kotonic acids	m. p. °C	Fatty acids	m. p., °C
n-Hexane	Eicosanoyl(C_{20})	27	$CH_3(CH_2)_{18}CO(CH_2)_6CO_2H$	99.5	Heptacosanoic	86.6(87)*
	Docosanoyl(C_{22})	29	$CH_3(CH_2)_{20}CO(CH_2)_6CO_2H$	101	Nonacosanoic	98.7(89.2)*
n-Octane		31	$CH_3(CH_2)_{20}CO(CH_2)_8CO_2H$	105	Hentriacontanoic	92.5
	Tetracosanoyl(C_{24})	33	$CH_3(CH_2)_{24}CO(CH_2)_8CO_2H$	107	Tritriacontanoic	96.0
n-Undecane	Tricosanoyl(C_{23})	35	$CH_3(CH_2)_{21}CO(CH_2)_{11}CO_2H$	109	Pentatriacontanoic	98.0
	Pentacosanoic(C_{25})	37	$CH_3(CH_2)_{23}CO(CH_2)_{11}CO_2H$	110	Heptatriacontanoic	98.7

* S. Shiina, *J. Soc. Chem. Ind. Jap.* (*Kogyo Kwagaku Zassi*), **39**, 345 (1936).

TABLE III

Starting materials		Intermediates				Products		Yields to bromides
Fatty acids			Alcohols	Bromides[a]	Malonic[b] acids	Fatty acids[c]		
	m. p. °C		m.p., °C	m.p., °C	m.p., °C		m. p., °C	%
Stearic	68.5	Octadecyl	58	28.5	109	Eicosanoic	75(75.5[d])	75
Behenic	79	Docosyl	71.5	44.0	125	Tetracosanoic	85(86.0[e])	50
Tricosanoic	78.5	Tricosyl	72.0	51.0	—	Pentacosanoic	83.5(85[e])	42

a) Bromination of the alcohols was modelled after Reid. [E. E. Reid et al., "Organic Syntheses" Vol. 15, John Willey & Sons, Inc., New York (1935), p. 26]. Hydrogen bromide was passed for 15 hr. in each alcohol.

b) Recrystallized from benzene.

c) The malonic acids were decarboxylated in vacuo and the resulting fatty acids were recrystallized from benzene.

d) F. Adam et al., *J. Chem. Soc.*, **1926**, 72.

e) P. A. Levene et al., *J. Biol. Chem.*, **59**, 921 (1924).

hydrogenation without purification, since it is known[2] that the compounds of this type can not be purified. Therefore, for the successful hydrogenation of the compounds, it is essential to purify the acid chlorides by distillation. However, since arachidyl and higher acid chlorides were found to decompose even under vacuum distillation at 2 mmHg, these acid chlorides were subjected to further reaction without distillation. In this case, oxalyl chloride proved to be superior for the preparation of acid chlorides to thionyl chloride because it furnished cleaner products. On hydrogenation considerable poisoning of the catalyst was found even when distilled acid chloride was used. After debenzylation and decarboxylation, the desired ketonic acids were obtained in low yield of about 35%, considerable amount of the starting fatty acids being recovered. Huang-Minlon reduction[6] of the ketonic acids took place readily to give the corresponding fatty acids which, after conversion to their ethyl esters, were led to the final products by reduction with lithium aluminum hydride.

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[6] Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2487 (1946).

Repeated recrystallizations of the alcohols from benzene or toluene gave products having sharp melting points and excellent analytical values. For hentriacontanol $C_{31}H_{63}OH$ and higher alcohols high vacuum distillation as well as recrystallization was employed. In order to prevent thermal degradation during distillation, the pressure was reduced to 2×10^{-3} mmHg so as to maintain the bath temperature below 210°C.

Melting points, transition points and analytical data of these alcohols are given in Table I. Heptatriacontanol $C_{37}H_{75}OH$ has not been reported previously. All the transition points have been unknown. Combination of the starting materials and the melting points of the intermediate ketonic acids and fatty acids are given in Table II. The physical properties of these alcohols are being investigated and the results will be reported in a separated communication.

Experimental

Preparation of ω-Bromo Acids and their Condensation with Ethyl Malonate. — *Ethyl ε-bromocaproate.*—It was prepared from caprolactone by the method described in Part I[1]. The physical constants are as follows: b. p. 118°C/14 mmHg or 98°C/4.5 mmHg, n_D^{32} 1.4561.

Ethyl ω-bromooctanoate.—The procedure of Hunsdiecker[3] was followed with some modification to give increased yield. Pure azelaic acid (m. p. 104~106°C) obtained by repeated recrystallizations of commercial specimen from aqueous ethanol was converted to its ethyl ester by exhaustive esterification. Boiling point of the ester was 135~137°C at 6.5 mmHg (reported: 130~132°C at 5 mmHg)[7]. Above acid (130 g.) and its ethyl ester (98 g.) were treated in the same manner as described in Organic Syntheses[8] for the preparation of ethyl hydrogen sebacate and yielded 62 g. of the monoester; b. p. 161 ~ 163°C/1 mmHg (reported: 169 ~ 170°C/2 mmHg)[9]. Silver salt of the monoester was prepared by an analogous manner described in Part I[1] for the preparation of silver heneicosanoate. The thoroughly dried silver salt (85 g.) was added portionwise to a solution of 60 g. of bromine in 100 ml. of carbon tetrachloride under strict exclusion of moisture. A vigorous reaction ensued with evolution of carbon dioxide. When no more gas evolved, the solution was filtered, washed with water, aqueous solution of sodium hydroxide, again water, and dried over sodium sulfate. Following evaporation of the solvent the residue was distilled through a short Widmer column to give a liquid having a boiling point of 125°C at 3.5 mmHg. n_D^{27}, 1.4572: Yield, 53 g. (80%), (reported: 69.7% for methyl compound)[3].

Ethyl ω-bromoundecanoate. — The preparation of the corresponding acid was essentially the same as the method described by Jones[4]. The melting point of the acid was 48~49.5°C (reported: 49~50°C).

Ethylester of the acid was obtained in an almost quantitative yield by exhaustive esterification. b. p. 148~150°C/5 mmHg, m. p. 11.5~13.5°C, n_D^{20} 1.4651.

The three ethyl esters of ω-bromo acids mentioned above were condensed with sodiomalonic ester by an usual method to give ethyl alkanetricarboxylates in good yields. The constants are: *Ethyl n-hexane-1, 1, 6-tricarboxylate* (II where *n* is 5): b. p. 150~151°C/1 mmHg, n_D^{28} 1.4360. *Ethyl n-octane-1, 1, 8-tricarboxylate* (II where *n* is 7): b. p. 170~172°C/1.5 mmHg, n_D^{28} 1.4380. *Ethyl n-undecane-1, 1, 11-tricarboxylate* (II where *n* is 10): b. p. 187°C/1 mmHg, n_D^{28} 1.4435.

Preparation of Long Chain Fatty Acids.—Except heneicosyl bromide which was prepared from behenic acid by degradative bromination[1], a long chain alkyl bromides were made by the reduction of the corresponding acid esters to the alcohols by high pressure hydrogenation or using lithium aluminum hydride followed by treatment with hydrogen bromide. Further treatment of the alkyl bromides with sodiomalonic ester in butanol[5] in place of ethanol led to the acids of two additional carbon atoms. Since these reactions are relatively well known, detailed descriptions of the experiments were omitted and the results are summarized in Table III.

Preparation of Higher Alcohols. — General procedures of the synthesis are very similar throughout the series, so only an example for the preparation of heptatriacontanol $C_{37}H_{75}OH$ is described in detail.

Benzyl n-undecane-1, 1, 11-tricarboxylate. — To a suspension of sodium ethoxide (prepared from 0.38 g. of freshly cut sodium and 10 ml. of absolute ethanol) in benzene was added 6.15 g. of ethyl undecane-1, 1, 11-tricarboxylate. After the sodium ethoxide dissolved 5.35 g. of purified benzyl alcohol was added, the mixture was distilled through a Fenske column until the boiling point reached to 80°C. During this time an almost theoretical quantity of ethanol was removed.

13-Keto-heptatriacontanoic acid $C_{24}H_{49}CO(CH_2)_{11}\cdot CO_2H$.—To the benzene solution of the above tribenzyl esters was added gradually 6 g. of pentacosanoyl chloride in benzene (prepared from 5.8 g. of pentacosanoic acid and 7.5 g. of oxalyl chloride, and excess of the oxalyl chloride was removed under reduced pressure at 100°C). The reaction mixture was refluxed for 1 hr. After cooling, the solution was washed with ice water to neutral reaction and then dried over sodium sulfate. The solvent was removed under reduced pressure at 50°C of bath temperature to give a brown colored oil which solidified on standing at room temperature. Yield, 20 g. Hydrogenation of the above compounds in 60 ml. of ethyl acetate over Pd-C (5 g.) and Pd-$SrCO_3$ (5 g.) took place at a slightly positive hydrogen pressure, accompanying a considerable poisoning of the catalysts. A nearly theoretical amount of hydrogen was absorbed within 3 hr. The catalyst was filtered off, then the ethyl acetate solution was refluxed for 1 hr. to decarboxylate compound V. Upon cooling to room temperature, small crystals were separated. They were recrystallized twice from ethyl acetate to give the product

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[7] Jones et al., *J. Chem. Soc.*, **1928**, 68.

[8] S. Swann, "Orgamic Syntheses", Vol. 19, John Wiley & Sons, Inc., New York (1938), p. 45.

[9] M. Asano, *J. Pharm. Soc. Japan*, **504**, 8 (1924).

having a melting point of 105 to 107°C. Further recrystallizations from benzene gave a pure acid. m. p. 108~109°C. Yield, 3.2 g. (37%). From the mother liquor, 2.5 g. of the pentacosanoic acid was recovered.

Heptatriacontanoic acid $C_{36}H_{73}CO_2H$.—The Hung-Minlon reduction of long chain ketonic acid was found to be superior to the Clemmensen reduction[4], because of its effectiveness and simplicity. The experimental conditions were essentially the same as those described in the first paper. A mixture of 3 g. of the ketonic acid, 3 g. of potassium hydroxide, 3 ml. of 85% hydrazine hydrate and 25 ml. of diethylene glycol (b. p. 250°C) was refluxed for 1 hr. After removing the water formed, the temperature of the mixture was gradually raised to 200°C and the refluxing was continued at this temperature for 6 hr. When the mixture was cooled to about 80°C. it was poured into a 100 ml. of water containing 15 ml. of hydrochloric acid with stirring. A white solid separated was collected and washed with water, and then dried. Yield of the crude acid was nearly quantitative. Repeated recrystallizations from benzene and then toluene gave a pure product with little loss of the material, m. p. 97.5~98.5°C.

Found: C, 78.42; H, 13.10. Calcd. for $C_{37}H_{72}O_3$: C, 78.66; H, 12.85%.

Heptatriacontanol $C_{37}H_{75}OH$.—Ethyl heptatriacontanoate (2.5 g.) was readily reduced to the alcohol with lithium aluminum hydride in absolute ether[1]. The reaction mixture was hydrolyzed to remove the small amount of unchanged ester, but traces of alkali or soap could not be removed from the product by crystallization. Pure alcohol could be obtained by high vacuum distillation at 2×10^{-3} mmHg followed by repeated crystallizations from toluene, m. p. 92~92.7°C. Yield, 1.8 g.

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